REMARKS

A copy of the undersign's file copy of pages 1, 2 and 3 of the application is attached hereto and it is requested that they be substituted for the PTO file pages to the extent necessary. The handwritten correction on page 1 are the amendments to this page submitted in the Amendment filed August 4, 1997. Accordingly, the attached pages are identical to the corresponding pages of the application as filed subject to said amendment.

The rejection of the claims under 35 U.S.C. §112 has been rendered moot by the foregoing amendment.

The rejection of the claims under 35 U.S.C. §103 over Cymbalista et al. in view of Hershenson '605 and Rideout '232 is respectfully traversed.

Claim 1 in this application sets forth a stable, liquid pharmaceutical formulation consisting of ß-IFN, a stabilizing amount of mannitol, a buffer maintaining the pH at between 3 and 4 and, optionally, albumin. This is neither taught nor suggested by the references whether considered alone or in combination.

The Cymbalista reference relates to a method of stabilizing ß-IFN with polyvinyl pyrrolidone (PVP). The only material taught to function as a stabilizer in this reference is the PVP. Note further that the stability data in this patent relates to the lypolized composition and not to the liquid formulation which exists either before or after lyophilization. Any conclusions concerning the stability of those liquid formulations based on the Cymbalista disclosure would be speculation.

It is alleged in the Final Rejection that it would be obvious to formulate a ß-IFN composition containing mannitol as the sole polyol because Cymbalista teaches mannitol stabilizes ß-IFN and exemplifies the preparation of a stable formulation comprising only one polyol. As to the first of these assertions, the Cymbalista reference has been carefully reviewed and no teaching which states or even implies that mannitol stabilizes ß-

IFN could be found. The Examiner did not identify any particular passage which contains this teaching and is respectfully submitted that no such teaching or suggestion exists.

As to the latter assertion, it is respectfully submitted that the characterization of mannitol as being a "polyol" constitutes a revision of the disclosure of the reference to such an extent that it has altered, impermissibly, the teachings of the reference. Medtronic, Inc. v. Cardiac Pacemakers, Inc., 220 USPQ 97 (Fed. Cir. 1983). There is nothing in the reference which characterizes mannitol as a polyol or indicates, for that matter, that the composition should contain a "polyol" for any purpose. Had Cymbalista said make a composition containing a polyol, then the fact that mannitol is a polyol may have had some significance, but there is no such teaching. The only function attributed to mannitol by Cymbalista is that of an excipient. While it is true that the reference "exemplifies the preparation of a stable formulation comprising only one polyol", it is respectfully submitted that this after-the-fact attempted justification is not relevant since Cymbalista teach that the only reason that the formulation is stable is that it contains PVP and does not suggest using a single polyol (even if an exemplified composition can be, by hindsight, so characterized).

It is respectfully submitted that the assertion in the Office Action that Hershenson also teaches that mannitol stabilizes ß-IFN is an overstatement of the disclosure in this reference. As the Examiner has recognized, this reference teaches that a stabilizing amount of either glycerol or polyethylene glycol (PEG) must be present and there is nothing in the reference which suggest that other materials (such as mannitol) can function as a stabilizer in the absence of either glycerol or PEG. In this connection, note that Hershenson teaches sucrose and human serum albumin enhances stability in the presence of glycerol or PEG while Cymbalista teaches that both sucrose and human serum albumin are ineffective as a stabilizing agent in their absence (see column 3, lines 1-3 and Tables 1-6).

The Office Action attempts to obviate the required presence of glycerol and PEG by asserting that "Cymbalista

evidences that such components were not necessary to obtain a stable IFN-ß formulation, and Hershenson contains no teachings to the contrary". However, to the extent it can be argued that the Cymbalista reference "evidences" such components are not necessary, it is only because the patentee uses PVP as a stabilizer. As to the asserted "no teachings to the contrary", it is respectfully pointed out that silence in a reference is an inadequate disclosure of facts upon which a conclusion of obviousness may justifiably follow. In re Burt, 148 USPQ 548 (CCPA 1966); In re Newell, 13 USPQ2d 1248, 1250 (Fed. Cir. 1989).

It is assumed that the Examiner is relying on the Rideout reference for the teaching that pharmaceutical formulations that contain IFN may be in the form of sterile, aqueous solutions that contain buffers and that these solutions may be sealed in ampules or vials, as set forth on page 5 of the May 1997 Office Action. No other relevancy to the rejection is apparent and it is clear, therefore, that this additional reference does not cure any of the basic deficiencies in Cymbalista or Hershenson, whether considered alone or in combination.

In light of the foregoing, it is respectfully submitted that this application is now in condition to be allowed and the early issuance of a Notice of Allowance is respectfully solicited.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on February 27, 1998:

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Name of applicant, assignee or Registered Representative

Signature

February 27, 1998

Date of Signature

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Respectfully submitted,

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IFN-β LIQUID FORMULATIONS

The present invention relates to liquid formulations of interferon-beta (IFN-β) stabilised with a polyol, a non-reducing sugar or an amino acid. In particular, it relates to liquid formulations containing mannitol, human albumin and acetate buffer.

Interferons (alpha, beta, gamma) are glycoproteins produced in the cells of vertebrates following induction. The most traditional inducers are virus, but also other microbial agents, other natural substances and synthetic compounds have the same behaviour.

Interferon-ß is induced in human fibroblasts, has anti-viral activity, but in the therapy of some tumoral forms, other activities can be exploited together with the anti-viral activity, such as the anti-proliferative cellular activity and immunoregulatory activity.

Production from culture of human fibroblasts, and specifically from recombinant DNA techniques, now allows to obtain industrial quantities of interferon-beta.

It is known that proteins in the purified form are especially susceptible to degradation, even due to the normal activity of atmospheric agents. This peculiarity becomes even more evident for proteins produced according to recombinant DNA techniques.

As a direct consequence of the fact that highly purified proteins are easily subject to denaturization, it becomes desirable to obtain stable formulations which ensure the longest possible life-cycle to the product.

Stabilisation of formulations containing highly purified proteins may be carried out by the addition of one or more excipients which inhibit or delay degradation of the active principle.

Pharmaceutical compositions containing interferon-beta are well known. EP Patent application 89 245 (INTER-YEDA Ltd) describes a lyophilised composition of interferon-beta containing mannitol, human albumin and polyvinylpyrrolidone, the latter as stabilising agent. Also known are pharmaceutical liquid compositions containing other interferons.

International Patent Application WO 89/04177 (GENENTECH - Priority 03/11/87) describes liquid pharmaceutical formulations of gamma-

interferon comprising a buffer which maintains the pH within the range of 4.0-6.0. a polyhydroxylate sugar as stabiliser and a non-ionic detergent.

EP Patent Application 270 799 describes IFN-β pharmaceutical compositions in liquid form or lyophilized, which comprise, as solubilizer/stabilizer, one or more non-ionic polymeric detergents.

It is highly desirable to obtain such liquid formulations in order to avoid the reconstitution of lyophilised preparations and thus to permit ease of use.

It has now surprisingly been found that liquid pharmaceutical formulations comprising interferon-beta stabilised with a polyol, a non-reducing sugar or an amino acid in an appropriate buffer result particularly stable and maintain biological activity for a long period of time.

The main object of the present invention is to provide a liquid pharmaceutical formulation comprising interferon-beta and a polyol, a non-reducing sugar or an amino acid, as stabiliser.

Preferably the stabiliser is selected from mannitol, saccharose and glycine; more preferably, the stabiliser is mannitol.

Preferably the liquid pharmaceutical formulation comprises a buffer with a pH between 3 and 4; more preferably, acetate buffer.

Another object of this invention is to provide a process for the preparation of such liquid pharmaceutical formulation comprising the stage of dilution of IFN-β with a solution of the excipients.

Yet another object of the present invention is to provide a presentation form of the liquid pharmaceutical formulation comprising the previously mentioned formulation, hermetically sealed under sterile conditions in a container suitable for storage prior to use.

To study the stability of liquid formulations of IFN-β, various formulations were prepared diluting bulk IFN-β in different buffers at varying pH, then storing the samples at different temperatures and carrying out assays with the immunological test at set intervals of time. Once the buffer solution and the preferred pH, with which the greater stability is obtained, have been selected, then the stabilised formulations of the invention are prepared by diluting the interferon bulk solution with the buffer solution containing also the excipients. Stability of the various formulations was determined by measuring the residual activity of IFN-β at

fixed intervals of time, after storage of the solution at the temperatures of 50°C, 37°C, and 25°C.

To determine such activity, samples were assayed under immunological and biological tests.

The immunological test was carried out by using the TORAY kit (Human IFN-Beta ELISA Kit, TORAY INDUSTRIES, Inc.), following the methodology reported in the enclosed instructions.

The biological dosage was performed as described by Armstrong J.A. (1981), Cytopathic effect inhibition assay for Interferon, in Methods in Enzymology 73 381-387. This test permits the measuring of IFN-β activity by exploiting its anti-viral capacity.

Measure of activity is expressed in International Units per millilitre of solution (IU/ml) or in Mega International Units per millilitre of solution (MIU/ml). (1 MIU/ml = 1,000,000 IU/ml).

An International Unit is calculated as described in the Research Reference Reagent Note No. 35, published by the National Institute of Health, Bethesda, Maryland, in relation to the HuIFN-beta NIH Reference Reagent Gb 23-902-531 used as standard.

The measurement is reported here as percentage of residual activity of the sample of Interferon-beta in the various formulations, taking activity of the sample at time zero as equal to 100%.

Dosages were carried out in duplicate.

To assess the effect of the pH on stability of the active ingredient, different formulations of recombinant IFN-β were prepared containing 0.6 and 1 MIU/ml with various buffer solutions, i.e. acetate buffer, citrate buffer, ascorbate buffer, succinate buffer.

The formulations containing recombinant IFN-β with the buffer solutions were prepared and stored at temperatures of 50°C, 37°C and 25°C, then assayed under the immunological test at set time intervals. The formulations were prepared in such a way as to have a pH between 3.0 and 4.0 and between 5.0 and 6.0, all with buffer at a concentration of 0.01 M.

Tables 1, 2 and 3 report results of tests carried out at set intervals of time, from 1 to 42 days, at the various temperatures.

Data contained in the above-mentioned tables indicate that the formulations with a pH between 5.0 and 6.0 show an immediate loss of